# Complete Summary

## GUIDELINE TITLE

Assessment: botulinum neurotoxin for the treatment of spasticity (an evidence-based review). Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology.

## BIBLIOGRAPHIC SOURCE(S)

Simpson DM, Gracies JM, Graham HK, Miyasaki JM, Naumann M, Russman B, Simpson LL, So Y, Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Assessment: Botulinum neurotoxin for the treatment of spasticity (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2008 May 6;70(19):1691-8. [48 references] PubMed

## GUIDELINE STATUS

This is the current release of the guideline.

## COMPLETE SUMMARY CONTENT



## SCOPE

### DISEASE/CONDITION(S)

Adult spasticity and spasticity in pediatric cerebral palsy

### GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Technology Assessment
Treatment

## CLINICAL SPECIALTY

Neurology
Orthopedic Surgery
Pediatrics
Pharmacology
Physical Medicine and Rehabilitation

## INTENDED USERS

Pharmacists
Physicians

## GUIDELINE OBJECTIVE(S)

- To perform an evidence-based review of the safety and efficacy of botulinum neurotoxin (BoNT) in the treatment of adult and childhood spasticity
- To make evidence-based recommendations

## TARGET POPULATION

Adults with spasticity and children with spasticity due to cerebral palsy

## INTERVENTIONS AND PRACTICES CONSIDERED

Botulinum neurotoxin (BoNT) injection

**Note**: BoNT has been approved for adult and childhood spasticity by regulatory agencies in many European countries, but has not yet been approved for these indications in the United States by the U.S. Food and Drug Administration.

## MAJOR OUTCOMES CONSIDERED

- Reduction in muscle tone
- Functional improvement

# METHODOLOGY

## METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Searches of Electronic Databases

## DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The literature search used MEDLINE and Current Contents for relevant, fully published, peer-reviewed articles up to April 2007 and was supplemented through manual searches by panel members. The search terms used were botulinum toxin and movement disorders, dystonia, tics, tremors, hemifacial spasm, blepharospasm, cerebral palsy, spasticity, autonomic, Frey's syndrome, sweating,

hyperhydrosis, drooling, headache, back pain, pain, laryngeal disorders, dysphonia, and urologic disorders. The following criteria were used: 1) relevant to the clinical questions of efficacy, safety, tolerability, or mode of use; 2) limited to human subjects; 3) limited to therapeutic studies. Abstracts, reviews, and meta-analyses were excluded.

## NUMBER OF SOURCE DOCUMENTS

Not stated

## METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

## RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

### Classification of Evidence for Therapeutic Intervention

**Class I**: Randomized, controlled clinical trial with masked or objective outcome assessment in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences. The following are required: a) concealed allocation, b) primary outcome(s) clearly defined, c) exclusion/inclusion criteria clearly defined, and d) adequate accounting for drop-outs (with at least 80% of enrolled subjects completing the study) and cross-overs with numbers sufficiently low to have minimal potential for bias.

**Class II**: Prospective matched group cohort study in a representative population with masked outcome assessment that meets b-d above OR a randomized controlled trial in a representative population that lacks one criteria a-d.

**Class III**: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement.*

**Class IV**: Studies not meeting Class I, II, or III criteria, including consensus, expert opinion, or a case report.

* Objective outcome measurement: An outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data).

## METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

## DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

The panel was comprised of specialists with experience in the therapeutic use of botulinum neurotoxin (BoNT) for the indications under consideration or with expertise in guideline methodology. Each article was reviewed by at least two panelists who did not participate in the trial reported. The articles were classified as Class I through IV using the American Association of Neurology (AAN) guideline process (see "Rating Scheme for the Strength of the Evidence"). Disagreements on article classification were resolved by discussion and consensus.

## METHODS USED TO FORMULATE THE RECOMMENDATIONS

Other

## DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Conclusions and recommendations were made according to the American Academy of Neurology (AAN) criteria for translating the quality of evidence for therapeutic interventions into recommendations.

## RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

### Classification of Recommendations

The strength of practice recommendations is linked directly to the level of evidence:

**Level A** = Established as effective, ineffective, or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.*)

**Level B** = Probably effective, ineffective or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or at least two consistent Class II studies.)

**Level C** = Possibly effective, ineffective or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies)

**Level U** = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven. (Studies not meeting criteria for Class I–Class III).

* In exceptional cases, one convincing Class I study may suffice for an "A" recommendation if 1) all criteria are met and/or 2) the magnitude of effect is large (relative rate improved outcome >5 and the lower limit of the confidence interval is >2.

## COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

## METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

## DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Draft guidelines were reviewed for accuracy, quality, and thoroughness by the American Academy of Neurology members, topic experts, and pertinent physician organizations.

The guideline was approved by the Therapeutics and Technology Assessment Subcommittee on March 31, 2007; by the Practice Committee on July 12, 2007; and by the American Academy of Neurology Board of Directors on January 30, 2008.

# RECOMMENDATIONS

## MAJOR RECOMMENDATIONS

Definitions of the levels of the recommendations (A, B, C, U) and classification of the evidence (Class I through Class IV) are provided at the end of the "Major Recommendations" field.

### Upper Extremity Spasticity and Lower Extremity Spasticity in Adults

*Conclusions*

Botulinum neurotoxin (BoNT) is established as effective in the treatment of adult spasticity in the upper and lower limb in reducing muscle tone and improving passive function (**14 Class I studies**). While relatively few studies examined active function, recent data suggest that BoNT is probably effective in improving active function (**one Class I study**). There are inadequate data to determine if electrical stimulation or electromyography (EMG) techniques for optimal muscle localization improves outcome.

*Recommendations*

- BoNT should be offered as a treatment option to reduce muscle tone and improve passive function in adults with spasticity (**Level A**), and should be considered to improve active function (**Level B**).
- There is insufficient evidence to recommend an optimum technique for muscle localization at the time of injection (**Level U**).

### Spasticity Due to Cerebral Palsy in Children

*Conclusions*

BoNT injection of the gastrocnemius-soleus muscles is established as effective in the treatment of spastic equinus in patients with cerebral palsy (CP) (**four Class I**

**studies**). There is insufficient evidence to support or refute the benefit of additional casting to BoNT injection of the gastrocnemius-soleus muscles (inconsistent Class II and III studies) and the injection of BoNT into the hamstrings (**only Class IV studies**). In patients with adductor spasticity, BoNT injection is probably effective in improving adductor spasticity and range of motion (**one Class I study**), as well as postoperative pain in children undergoing adductor muscle lengthening surgery (**one Class I study**). In patients with upper extremity symptoms, BoNT injection is probably effective in improving spasticity and range of motion (**two Class II studies and one Class III study**).

*Recommendations*

- BoNT injection of the calf muscles should be offered as a treatment option for equinus varus deformity in children with cerebral palsy (**Level A**).
- BoNT injection should be considered as a treatment option for treatment of adductor spasticity and for pain control in children undergoing adductor-lengthening surgery (**Level B**).
- BoNT injection should be considered as a treatment option in children with upper extremity spasticity (**Level B**).

**Definitions:**

**Classification of Recommendations**

**Level A** = Established as effective, ineffective, or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies*)

**Level B** = Probably effective, ineffective, or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.)

**Level C** = Possibly effective, ineffective, or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)

**Level U** = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven. (Studies not meeting criteria for Class I–III.)

*In exceptional cases, one convincing Class I study may suffice for an "A" recommendation if 1) all criteria are met, 2) the magnitude of effect is large (relative rate improved outcome >5 and the lower limit of the confidence interval is >2.

**Classification of Evidence for Therapeutic Intervention**

**Class I**: Randomized, controlled clinical trial with masked or objective outcome assessment in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences. The following are required: a) concealed allocation, b) primary outcome(s) clearly defined, c) exclusion/inclusion criteria clearly defined, and d) adequate accounting for drop-outs (with at least

80% of enrolled subjects completing the study) and cross-overs with numbers sufficiently low to have minimal potential for bias.

**Class II**: Prospective matched group cohort study in a representative population with masked outcome assessment that meets b-d above OR a randomized controlled trial in a representative population that lacks one criteria a-d.

**Class III**: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement.*

**Class IV**: Studies not meeting Class I, II, or III criteria, including consensus, expert opinion, or a case report.

* Objective outcome measurement: An outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data).

### CLINICAL ALGORITHM(S)

None provided

## EVIDENCE SUPPORTING THE RECOMMENDATIONS

### TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for each recommendation (see "Major Recommendations").

## BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

### POTENTIAL BENEFITS

Appropriate use of botulinum neurotoxin for treatment of adult and pediatric spasticity

### POTENTIAL HARMS

- Undesirable effects associated with administration of botulinum neurotoxin (BoNT) fall into three broad categories. First, diffusion of the toxin from the intended sites of action can lead to unwanted inhibition of transmission at neighboring nerve endings. Second, sustained blockade of transmission can produce effects similar to anatomic denervation, including muscle atrophy. The third undesirable effect is immunoresistance to BoNT.
- Adverse events reported for BoNT in the treatment of spasticity include:
    - Focal weakness
    - Pain
    - Falls
    - Incontinence

- Dysphagia

## QUALIFYING STATEMENTS

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This statement is provided as an educational service of the American Academy of Neurology (AAN). It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN recognizes that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved. The clinical context section is made available in order to place the evidence-based guideline(s) into perspective with current practice habits and challenges. No formal practice recommendations should be inferred.

## IMPLEMENTATION OF THE GUIDELINE

### DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

### IMPLEMENTATION TOOLS

Patient Resources
Quick Reference Guides/Physician Guides
Slide Presentation
Staff Training/Competency Material

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

## INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

### IOM CARE NEED

Getting Better
Living with Illness

### IOM DOMAIN

Effectiveness
Patient-centeredness
Safety

## IDENTIFYING INFORMATION AND AVAILABILITY

### BIBLIOGRAPHIC SOURCE(S)

Simpson DM, Gracies JM, Graham HK, Miyasaki JM, Naumann M, Russman B, Simpson LL, So Y, Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Assessment: Botulinum neurotoxin for the treatment of spasticity (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2008 May 6;70(19):1691-8. [48 references] PubMed

### ADAPTATION

Not applicable: The guideline was not adapted from another source.

### DATE RELEASED

2008 May 6

### GUIDELINE DEVELOPER(S)

American Academy of Neurology - Medical Specialty Society

### SOURCE(S) OF FUNDING

American Academy of Neurology (AAN)

### GUIDELINE COMMITTEE

Therapeutics and Technology Assessment Subcommittee

### COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

*Primary Authors*: D.M. Simpson, MD; J-M. Gracies, MD, PhD; H.K. Graham, MD; J.M. Miyasaki, MD, Med; M. Naumann, MD; B. Russman, MD; L.L. Simpson, PhD; Y. So, MD, PhD

### FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

The American Academy of Neurology (AAN) is committed to producing independent, critical and truthful clinical practice guidelines (CPGs). Significant efforts are made to minimize the potential for conflicts of interest to influence the recommendations of this CPG. To the extent possible, the AAN keeps separate those who have a financial stake in the success or failure of the products appraised in the CPGs and the developers of the guidelines. Conflict of interest forms were obtained from all authors and reviewed by an oversight committee prior to project initiation. AAN limits the participation of authors with substantial conflicts of interest. The AAN forbids commercial participation in, or funding of, guideline projects. Drafts of the guidelines have been reviewed by at least three AAN committees, a network of neurologists, *Neurology* peer reviewers, and

representatives from related fields. The AAN Guideline Author Conflict of Interest Policy can be viewed at www.aan.com.

The authors report the following conflicts: Dr. Simpson has received speaker honoraria and research support from Allergan, Merz, and Solstice, Inc., and performs botulinum toxin injections. Dr. Gracies has received speaker honoraria and research support from Allergan, Merz, and Solstice, Inc. Dr. Graham has received speaker honoraria and research support from Allergan and performs botulinum toxin injections. Dr. Miyasaki has received research support from Boehringer Ingelheim, Huntington Study Group, NIH, Solvay, Solstice, and Teva. Dr. Naumann has received speaker honoraria from Ipsen and Allergan and performs botulinum toxin injections. Dr. Russman has received research support from Allergan and performs botulinum toxin injections. Dr. L. Simpson has received research support from Allergan. Dr. So holds financial interest in Satoris Inc., and has received research support from NIH, Pfizer, Inc., and NeurogesX, Inc.

## ENDORSER(S)

American Academy of Physical Medicine and Rehabilitation - Medical Specialty Society

## GUIDELINE STATUS

This is the current release of the guideline.

## GUIDELINE AVAILABILITY

Electronic copies: A list of American Academy of Neurology (AAN) guidelines, along with a link to a Portable Document Format (PDF) file for this guideline, is available at the AAN Web site.

Print copies: Available from the AAN Member Services Center, (800) 879-1960, or from AAN, 1080 Montreal Avenue, St. Paul, MN 55116.

## AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Use of botulinum neurotoxin for the treatment of spasticity. AAN summary of evidence-based guidelines for clinicians. St. Paul (MN): American Academy of Neurology. 2008. 2 p. Available in Portable Document Format (PDF) from the American Academy of Neurology Web site.
- Assessment: botulinum neurotoxin for the treatment of autonomic disorders and pain, movement disorders, and spasticity (an evidence-based review). Slide presentation. St. Paul (MN): American Academy of Neurology. 2008. 146 p. Available from the AAN Web site.
- Assessment: botulinum neurotoxin for the treatment of autonomic disorders and pain, movement disorders, and spasticity (an evidence-based review). Case study and coding. St. Paul (MN): American Academy of Neurology. 2008. 3 p. Available from the AAN Web site.

- AAN guideline development process [online]. St. Paul (MN): American Academy of Neurology. Available from the AAN Web site.

### PATIENT RESOURCES

The following is available:

- Use of botulinum neurotoxin injections to treat spasticity. AAN summary of evidence-based guideline for patients and their families. St. Paul (MN): American Academy of Neurology (AAN). 2008. 2 p.

Electronic copies: Available in Portable Document Format (PDF) from the AAN Web site.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

### NGC STATUS

This summary was completed by ECRI Institute on October 31, 2008. The information was verified by the guideline developer on December 30, 2008.

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